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Arthritis, Rheumatic Diseases, and Related Disorders

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NATIONAL INSTITUTES OF HEALTH

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases

ARTHRITIS, RHEUMATIC DISEASES, AND RELATED DISORDERS

Arthritis can affect not only the joints but also other connective tissues of the body. These tissues include important supporting structures such as muscles, tendons, and ligaments, as well as the protective coverings of internal organs. Strictly speaking, the word "arthritis" means joint inflammation, although it is often used more broadly to indicate any joint or connective tissue disorder. These disorders--of which there are more than 100--are also frequently referred to as the rheumatic diseases.

At present, rheumatic diseases affect more than 37 million Americans--approximately 1 in 7. Arthritis, the Nation's number one crippler, can afflict people of all ages, including children and adults in the prime of life.

A full understanding of many forms of arthritis remains elusive, but research has brought us closer to answering important questions about these disorders and, in some cases, has provided effective means to treat, control, or prevent them, or to reduce their harmful effects.

Major advances in arthritis research over the years include:

- identifying the cause of and developing a treatment for Lyme disease, a form of arthritis that has been found to be caused by a newly recognized infectious agent.

- improved survival rates for systemic lupus erythematosus (SLE or lupus), an inflammatory disease of the connective tissue that can affect many parts of the body, including the joints, skin, and internal organs.

- the finding that additional calcium and estrogen replacement in postmenopausal women may halt or retard the progress of osteoporosis. This disease, characterized by decreased bone mass, causes an estimated 1.3 million fractures annually in people 45 years of age or older.

- remarkable clinical advances in total hip-joint replacement that have led to the development of replacements for other diseased or damaged joints that are sources of pain and disability. Today, abnormal alignment of joints can be corrected and tendons and ligaments can be repaired.

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The National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases (NIADDK) leads and coordinates the Federal biomedical research effort against the many forms of arthritis and related disorders. Through its extramural programs of grants and contracts, the Institute supports research projects at universities, medical schools, and other research institutions throughout the country. In addition, NIADDK conducts an intensive intramural research program at the Warren G. Magnuson Clinical Center of the National Institutes of Health (NIH).

NIADDK RESEARCH HIGHLIGHTS

Although medical science has not yet found a cure for many types of arthritis, significant progress has been made through both basic and clinical investigations.

Rheumatoid Arthritis

The major crippling disorder among the chronic rheumatic diseases, rheumatoid arthritis (RA) affects more than 7 million Americans. This chronic inflammatory disease of unknown cause affects twice as many women as men. The primary target of rheumatoid arthritis is the synovium (joint lining). This tissue, which normally should be smooth and shiny, becomes inflamed, painful, and swollen. Rheumatoid arthritis is also a systemic disease that can cause general symptoms such as weakness, fatigue, and loss of appetite. RA tends to be both chronic and irregular, and can be very disabling.

In research on new effective therapies for rheumatoid arthritis, NIADDK grantee Dr. Michael E. Weinblatt and colleagues at Beth Israel Hospital in Boston have shown that low doses of methotrexate--the anticancer drug used to treat patients with psoriasis and psoriatic arthritis--suppress the inflammation of rheumatoid arthritis. Twenty-eight patients with severe rheumatoid arthritis who had not responded to conventional therapy received either methotrexate or a placebo for 24 weeks. Although no remission of the arthritis was reported, the methotrexate group had significant reductions in the number of swollen joints, as compared to the placebo group. These findings corroborate results from an NIADDK multicenter study led by Dr. John Ward at the University of Utah in Salt Lake City.

A new animal model for rheumatoid arthritis may provide new insights into the causes of this disease. Researchers at the University of Alabama in Birmingham led by Drs. William J. Koopman and Francis X. O'Sullivan have developed an animal model that spontaneously develops a disease resembling human rheumatoid arthritis. Their studies of these mice have suggested that joint destruction can occur before there is any evidence of joint inflammation.

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A substance found in the nervous system may play an important role in promoting the inflammatory component of arthritis. In a study of rats with an experimentally induced arthritis similar to rheumatoid arthritis in humans, grantee Dr. Jon Levine and associates at the University of California at San Francisco and also at Massachusetts General Hospital in Boston found that the severity of arthritis can be attributed to actions of "substance P" in the affected joint. Substance P, produced by nerve endings, is involved in transmission of pain signals. The researchers believe that measures designed to block and reduce substance P levels in joints may effectively combat both inflammation and tissue destruction.

Osteoarthritis

More than 16 million Americans are afflicted with degenerative joint disease or osteoarthritis. This most common form of arthritis primarily affects the cartilage of the joint, causing it to fray, wear, ulcerate, and, in extreme cases, to disappear, leaving a bone-on-bone joint. At the edges of the joint, spurs may form. Disability most often results from osteoarthritis of the weight-bearing joints (knees, hips, and spine).

To focus more attention on research on osteoarthritis, a workshop was held in July 1985, sponsored by the NIADDK, the National Institute on Aging, and voluntary health organizations, including the American Academy of Orthopaedic Surgeons and the Arthritis Foundation. Experts in epidemiology, anatomy and pathology, biochemistry, biomechanics, inflammation, and clinical medicine assessed current knowledge of osteoarthritis and suggested research directions.

Investigators are using a variety of approaches to understand better why and how osteoarthritis occurs. NIADDK grantee Dr. Nancy Lane and associates at Stanford University in Stanford, California, are studying 550 members of the Over 50 Runners Club who have run an average of 9,983 total miles each. The researchers have compared a subset of the runners with a group of nonrunners in the same age range. Preliminary results indicate that running does not seem to play a role in the development of osteoarthritis. However, running does foster an increase in bone density, according to the study.

Juvenile Arthritis

Although arthritis is commonly viewed as an affliction of adults, an estimated 250,000 children in the United States are also afflicted. The first cooperative medical project on the treatment of children with arthritis was conducted recently in both the United States and Russia. This study was designed to

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evaluate the safety and effectiveness in children with arthritis of two powerful slow-acting drugs ordinarily used in adults with arthritis. NIADDK grantee Dr. Earl Brewer at Texas Children's Hospital, Houston, reported that although more than half of the children taking these compounds--penicillamine and hydroxychloroquine (an antimalarial drug)--improved, a similar number of patients taking placebo and milder non-steroidal anti-inflammatory drugs also improved. Additional studies in children with rheumatoid arthritis are already under way to examine the therapeutic effect of a new oral gold compound, auranofin.

Lupus

According to the Lupus Foundation of America, there are more than 500,000 people, primarily young women, in the United States with the disease. The exact cause of lupus is unknown, but evidence suggests that the disease may result from a disorder in the body's production of antibodies (proteins that fight invading organisms). In lupus, abnormal antibodies are produced that react against the patient's own tissues.

Researchers led by Dr. David Wofsy, University of California, San Francisco, are studying abnormal immune responses in lupus. In studies of mice with lupus, they found that the course of the disease can be improved through the use of highly specific monoclonal antibodies that can remove a subset of immune cells known as helper T cells. The researchers hypothesize that these helper T cells may promote the abnormal immune reactions in lupus and that, ultimately, anti-T-cell antibodies may be able to retard SLE development in humans.

In studies of the genetic aspects of lupus, Dr. Betty Diamond, a grantee at Albert Einstein College of Medicine, Yeshiva University, New York, is using monoclonal antibodies to analyze antibodies to DNA, the substance of heredity. Antibody to native DNA is considered to be specific for lupus and is found in most lupus patients. In studies of familial lupus, she and her colleagues have shown that there may be a genetic predisposition or an inherited defect that causes genes to encode anti-DNA antibodies.

Scleroderma

Scleroderma is characterized by excessive deposits of the structural protein collagen in the skin and various other organs such as the heart, kidneys, lungs, and gastrointestinal tract. These deposits can cause thickening and hardening of the affected organs. Effects of the disease range from mild to life-threatening.

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NIADDK grantee Dr. Sergio A. Jimenez and associates at the University of Pennsylvania, Philadelphia, are studying the usefulness of gamma interferon produced by recombinant DNA technology in treating patients with scleroderma. (Gamma interferon is one form of interferon, a protein made by the body's immune system to help combat certain diseases.) Skin cells were removed from patients who had had active scleroderma for less than 1 year and from normal persons. Scleroderma cells showed increased collagen production when compared with normal cells. When the researchers added gamma interferon to both cell lines, all cells showed a reduction of collagen. These results indicate that gamma interferon may provide a possible treatment for patients with this incurable disease.

Orthopedic Research and Related Diseases

Back Disorders

Low-back pain is a major medical disorder that affects 50 to 80 percent of the United States population and causes an economic burden thought to exceed $10 billion annually. Back injuries due to improper lifting and handling of materials are a significant cause of work-related disability and account for a large amount of workers' compensation expenditures in the United States.

Investigators led by Dr. Matthew Liang at Boston's Brigham and Women's Hospital are studying how low-back injuries can be prevented at the worksite by evaluating lifting practices of more than 4,500 Boston postal workers and their supervisors. The ultimate goals of the study are to reduce the incidence of lifting-related back injuries and the subsequent loss of work time.

While the above study relates primarily to injuries associated with the manual handling of materials, grantees Drs. Ian Stokes at the University of Vermont, Burlington, and Vijay Goel at the University of Iowa, Iowa City, are studying how repetitive mechanical loading on joints, bones, ligaments, tendons, and muscles of the back relates to the development of osteoarthritis, fractures, and other musculoskeletal injuries.

Osteoporosis

Osteoporosis, a major health problem, affects an estimated 15 to 20 million Americans. According to a recent report by Dr. Jennifer Kelsey, Yale University, New Haven, Connecticut, the total cost of osteoporosis and osteoporotic fractures in 1983 was an estimated $6.1 billion in the United States.

Researchers led by Dr. B. Lawrence Riggs at the Mayo Clinic in Rochester, Minnesota, recently compared the effects of menopause-caused estrogen deficiency to the effects of aging on bone loss. The researchers measured bone density in three

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groups of women: normal women in their early fifties at or before menopause (perimenopausal): normal postmenopausal women in their early seventies; and women of average age 54 who had undergone bilateral oophorectomy (surgical removal of both ovaries) 15 to 25 years earlier. The scientists found the same amount of bone loss in the oophorectomized women in their fifties as in postmenopausal women in their seventies. Both groups had significant bone loss compared to that of the perimenopausal women in their fifties. According to Dr. Riggs, estrogen deficiency, not aging, is the predominate cause of osteoporosis during the first two decades after natural menopause.

A common feature of osteoporosis is crush fractures of the vertebrae (the bony segments of the spine). Dr. Edmund Y.S. Chao and associates at the Mayo Clinic, Rochester, Minnesota, have developed a new biplanar x-ray method to measure and monitor geometric shape changes in the vertebrae of osteoporotic patients. Information from the x-rays is fed into a computer for calculation of vertebral configuration and for future comparison. The researchers said that it is important to quantitate vertebral changes accurately so that they can be related to the progression of the disease and the efficacy of treatment.

Osteogenesis Imperfecta (OI)

OI, an inherited disease, is characterized by fragile bones that fracture easily. Many people with the disease have multiple fractures throughout their lifetimes. Some children are born with fractures; others have their first fractures within a few months or years after birth.

A defect in collagen is generally accepted as a major factor in the development of OI. Researchers led by Dr. Darwin Prockop at Rutgers Medical School in Piscataway, New Jersey, are using new technology (cDNA probes) to advance understanding of the molecular defects in the genes that determine collagen structure. In many patients with OI, the collagen fibers are malformed and misoriented. The researchers hope to identify possible gene defects in both parents and offspring, even before birth, and to develop methods to replace defective collagen genes.

Because OI bone is so fragile, the most common method of treatment is to reinforce it with a supporting rod that keeps the bone straight. In order to evaluate how much force can be applied to the bone and utilize the best method to strengthen it, Dr. Peter Frasca and colleagues at Thomas Jefferson University, Philadelphia, have developed a new procedure to evaluate mechanically OI bone as compared to normal bone.

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Exercise Pathophysiology

With growing national interest in exercise and fitness, new efforts are being directed toward understanding the responses of the body to various forms of exercise and physical training.

Dr. Ronald Terjung and associates at Upstate Medical Center, Syracuse, New York, are studying the biochemical and physiological influences of exercise training on muscle. Muscle performance is influenced by its type (fast- or slow-contracting) and its biochemical capacity for oxygen consumption. Muscle fatigue and its recovery vary in different types of muscle. Slow-conracting muscles, for example, recover from fatigue in less than 1 minute. In contrast, fast-contracting muscles require approximately 1 hour to recover. Dr. Terjung and his team have found that as a result of conditioning, fast muscles convert to slow muscles and recover from exercise more rapidly. This finding helps to explain the increased resistance to fatigue in well-trained athletes.

Knowledge gained from these basic studies of muscle physiology may eventually lead to the optimal rehabilitation programs, and to more efficient training programs for athletes.

As increasing numbers of children engage in strenuous and competitive programs such as long-distance running, a potential concern is the long-term effect on growing bones and joints. Dr. Vittorio Pedrini-Mille and associates at the University of Iowa, Iowa City, recently completed a study to determine the effects of strenuous exercise on young knees. Researchers chose the chicken as the research model because chicken menisci (shock absorbing tissues within the knee) are similar to those of humans. The scientists found no ill effect on menisci of growing chickens who were put on a 6-week treadmill-running regimen and no significant difference between the running animals and their sedentary controls.

New Developments in Joint Replacements

Total replacement of severely diseased or injured joints in the body has become a common and successful orthopedic treatment for arthritis, fractures, and related conditions. An NIH Consensus Development Conference on Total Hip-Joint Replacement reported a 90 percent success rate 10 years after implantation. However, after many years, failures of the prosthesis due primarily to loosening have become increasingly common. Loosening of the implant is often accompanied by resorption of bone adjacent to the surgical cement. Researchers led by Dr. Myron Spector at Emory University, Atlanta, Georgia, are studying the use of cementless attachments of hip prosthesis. The most common approach is the use of porous materials to permit bone to grow into the stem of the prosthesis and thus provide a more permanent attachment than cemented devices.

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Another approach to the problem of loosened hip-joint replacements is the use of computer modeling to reconstruct mathematically the exact geometry of a particular femur (thigh bone). Researchers led by Dr. Peter S. Walker at Brigham and Women's Hospital, Boston, in their studies of cadaver femurs, showed that implanting an "exact-fit" prosthesis produced close to normal bone stress with minimal micromotion (motion between implant and bone). The scientists are beginning to apply this valuable information to custom-design of hip implants for younger patients, those with abnormal bone shapes, or those who had a prosthesis "fail." Similar techniques are also being applied to the design of knee joint replacements.

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National Cancer Institute

In rheumatoid arthritis, tissue from the lining of bony joints proliferates and destroys the cartilage, bone, and tendons of the joints.

At the Dartmouth-Hitchcock Medical Center in Hanover, New Hampshire, Dr. Constance Brinckerhoff and colleagues, with support from the National Cancer Institute and the NIADDK, have been studying how retinoids--a family of compounds, including both natural and synthetic forms of vitamin A--inhibit collagenase production. Collagenase, an enzyme produced by connective tissue, is believed to play a role in rheumatoid arthritis. Dr. Brinkerhoff has found that, in animals and in animal cells grown in the laboratory, retinoids inhibit the production of collagenase even in the presence of factors that usually increase enzyme production.

In other work on growth factors, Dr. Brinckerhoff has looked specifically at the role of transforming growth factors in arthritis. Transforming growth factors play a role in turning normal cells into malignent ones but are found also in embryonic and some normal tissues. Dr. Brinckerhoff and colleagues have shown that the addition of transforming growth factors to laboratory cultures of normal cells from joints and connective tissue caused the cells to grow rapidly and pile up in a pattern characteristic of cultured human rheumatoid arthritis cells. This finding also applies to other cells in the joints that may play a role in rheumatoid arthritis.

Dr. Brinckerhoff's group has also reported that gamma interferon produced by recombinant DNA technology increased cell division in cultures of normal cells from joints. This activity was enhanced by the anti-inflammatory drug prednisolone but blocked by the addition of a retinoid. Because gamma interferon is secreted by white blood cells called T cells, which are found in inflamed arthritic tissues, these findings may be relevant to the treatment of rheumatoid arthritis.

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National Institute of Dental Research

The National Institute of Dental Research (NIDR) conducts and supports research related to arthritis because certain dental problems such as periodontal diseases have factors in common with diseases of the joints such as arthritis. In addition, the NIDR investigates chronic, acute, and inherited disorders of the human skeletal system.

NIDR intramural scientist Dr. Sharon Wahl is investigating why the tissues of arthritis patients are susceptible to chronic inflammation. Her studies of patients with chronic rheumatoid arthritis show that their monocytes (blood cells that surround and kill infection-causing agents) do not migrate as they normally would toward inflammatory stimuli. Dr. Wahl has also discovered that, in a subpopulation of these patients, the cells responsible for inflammation in the tissue surrounding joints produce excess amounts of lymphocyte derived chemotactic factor, an agent that attracts monocytes. When the monocytes reach the inflamed joint, they in turn release several agents that enhance and perpetuate inflammation. One of these agents is fibroblast activating factor (FAF), a product of activated T cells. FAF stimulates the development of fibrous tissue, which, in turn, causes the release of prostaglandins and collagenase, which causes the degeneration of the joint. Dr. Wahl is now studying FAF in an effort to understand how rheumatoid arthritis develops. In collaboration with NIADDK scientists, Dr. Wahl has demonstrated that the development of erosive polyarthritis and hepatic granulomas (tumor-like masses of cells due to chronic inflammation) in rats treated with bacterial cell walls is dependent upon T cells. Rats treated with the T cell inhibitor, cyclosporin A, and athymic rats that are deficient in T cells do not develop chronic inflammatory arthritis or granulomas.

In studies of how genes regulate the development and function of connective tissue, NIDR intramural scientists Drs. Yoshihiko Yamada and John Termine and their colleagues have isolated DNA clones for some of the genes that produce cartilage and bone. This approach has been useful in determining the structure of cartilage and bone components. Molecular probes such as these can be used to measure levels of both collagenous and noncollagenous bone components in normal, developing, and diseased skeletal tissue. Studies are also under way to inject collagen genes into mouse embryos that lack cartilage collagen and to incorporate cartilage collagen DNA into degenerating and normal cartilage cells. These molecular biology studies are essential for understanding the genetic basis of metabolic diseases of cartilage and bone, and may eventually lead to strategies for their diagnosis and treatment.

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Proteoglycans are agents that are essential to the cushioning function of cartilage. NIDR intramural scientist Dr. Vincent Hascall and his associates are investigating both the chemical and physical properties and the biosynthesis of proteoglycans and other cartilage components in cell and tissue systems. In particular, he is studying how the components interact with each other, as well as what regulates the synthesis and turnover of the proteoglycans. Dr. Srinivasan Chandrasekhar, an NIDR scientist, has identified a collagen binding protein that regulates the size of the collagen fibers in cartilage. These studies have significant bearing on degenerative diseases such as arthritis, the early stages of which result in degradation and altered synthesis of cartilage.

NIDR's Dr. Valerie Horn and colleagues have been using monoclonal atnibodies to develop an assay for levels of chondronectin in blood. Chondronectin is a glycoprotein which, in cartilage, binds the cells to the surrounding matrix through interactions with the collagen and proteoglycans. Early data suggest that such a test will be a valuable diagnostic tool for measuring the metabolism of cartilage, and perhaps for identifying cartilage disease in the early stages.

In another NIDR intramural investigation, Dr. Haridara Reddi is studying the local and systemic control of bone development by bone matrix substances. He has identified and characterized the factor in bone matrix that is responsible for the formation of new bone. By learning more about how bone heals itself when fractured, scientists may discover ways to accelerate the healing process as well as determine how degenerative disease undermines the normal healing process.

Dr. Pamela Robey, NIDR intramural scientist, has been investigating how serum from young and aging human individuals affects bone cells isolated either from young or old persons. Her studies demonstrate marked metabolic changes in bone cells as aging occurs. Such studies provide models for investigating molecular mechanisms operative in both bone degeneration and the aging processes.

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National Institute of Neurological and Communicative Disorders and Stroke

In addition to studies of the central nervous system, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) supports research on the interaction of the nervous system with the normal and abnormal function of the neuromuscular and immune systems. These studies seek basic information on how muscles, joints, nerves, and other neuromuscular components function in relation to each other, knowledge that may lead to a better understanding of some forms of arthritis.

Dr. Marinos Dalakas, an NINCDS intramural scientist, is investigating the structure and electrophysiological function of cells to determine the effects of aging on neuromuscular systems. He has identified structural changes in the muscles of older individuals that may be similar to changes caused by arthritis. Dr. Dalakas has also found metabolic or immune abnormalities in the muscles, nerves, brains, and spinal fluids of patients with polyneuropathy and amyotrophic lateral sclerosis, diseases, like arthritis, that are characterized by muscle weakness.

NINCDS intramural scientist Dr. Edward Oldfield is studying Cushing's disease, a disorder of the body's hormone secreting system caused by pituitary tumors. Cushing's disease resembles arthritis in its characteristic muscle weakness. Dr. Oldfield, in collaboration with investigators in Dr. Lynn Loriaux's laboratory in the National Institute of Child Health and Human Development (NICHD), is studying how chemical "releasing factors" in the brain's hypothalamus influence the release of hormones in the pituitary gland. Improved understanding of this process should help scientists develop new therapies for diseases affecting neuromuscular function.

Other NINCDS-supported studies focus on the treatment of chronic pain, another primary symptom of arthritis. This year, Dr. Judith Turner, a grantee at the University of Washington in Seattle, began an evaluation of two methods for treating chronic back pain. The first method combines training in relaxation techniques with teaching patients to recognize emotional factors affecting pain. The second combines exercise with instruction on how to modify behavior to reduce pain. Findings from these studies could apply to all types of chronic pain patients, including those who suffer from arthritis.

At Case Western Reserve University in Cleveland, Ohio, NINCDS grantee Dr. Terrone Rosenberry is studying the structural and biosynthetic relationships of several forms of the enzyme acetylcholinesterase (AChE). Dr. Rosenberry has found that the AChE in neuromuscular tissues around joints

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is accompanied by a material similar to collagen. The AChE found in other muscle membranes has no collagen. Dr. Rosenberry plans to analyze the amino acid sequence of human red blood cell AChE and compare it with other known types of AChE to learn more about how the neuromuscular system works.

NINCDS grantee Dr. Peter Grigg, at the University of Massachusetts Medical School in Worcester, is studying normal and deformed collagen structure in rats to determine its mechanical relationship to other molecules in joints. In another animal study, Dr. Grigg is investigating how neurons carry messages to the knee joint. His work will help explain what factors are involved in the body's response to stimuli.

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National Institute of Allergy and Infectious Diseases

Arthritis-related research conducted and supported by the National Institute of Allergy and Infectious Diseases (NIAID) focuses on normal and abnormal functions of the immune system, factors involved in inflammation, the possible role of infectious agents, and the influence of genetics.

The immune system is a complex network of organs and specialized cells that mobilize to fight infection. It produces two major classes of cells--B cells, which secrete antibodies, and T cells, which help regulate antibody production. Sometimes the immune response turns against the body's normal tissues and results in what are called autoimmune diseases.

Lupus is a serious and complex autoimmune disease that is characterized in part by enhanced B cell activity and an excess of antibody. Intramural scientist and NIAID Director Dr. Anthony Fauci and colleagues have purified and characterized a specific B cell growth factor that may be important in B cell activation. In addition they found that interleukin-2, a T cell growth factor, also enhances B cell proliferation and antibody production. These studies will help clarify exactly how B cell activation occurs and how it differs in normal and disease states.

NIAID scientist Dr. Michael Frank and colleagues have developed a test that may provide further clues about the causes of a number of autoimmune diseases, including lupus, Guillain-Barre syndrome, and multiple sclerosis. The test detects the activation of a group of proteins, called complement, in the spinal fluid of patients with central nervous system symptoms related to these diseases. These proteins, which normally fight bacteria, damage normal tissues in these patients. This discovery may provide a diagnostic test to distinguish brain diseases due to autoimmunity from brain diseases due to other causes.

NIAID intramural scientists under the direction of Dr. Thomas Chused are studying inbred mice that spontaneously develop an autoimmune disorder closely resembling SLE. They have found that, in the New Zealand black mouse, certain T cells (which suppress the production of antibodies by B cells) enlarge in size just before the disease develops. Enlargement of these cells correlates with their impaired ability to suppress inappropriate autoimmune responses, and the immune system begins to attack normal body tissue.

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Some B cells in New Zealand black mice are also abnormal, spontaneously producing antibodies when no disease organism is present. Dr. Chused and colleagues have identified a combination of several abnormal genes that cause these defects in the T and B cells and lead to autoimmune disease. They have also isolated a previously unknown protein in the affected cells.

Much human autoimmune disease is probably caused by the interaction of several genes. Identification of the genes that cause these abnormal functions of T and B lymphocytes in humans and the development of methods to detect them in patients will lead to improved diagnosis and treatment of human autoimmune disorders.

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National Institute of General Medical Sciences

The National Institute of General Medical Sciences (NIGMS) supports basic research and research training that provide the foundation for a better understanding of fundamental life processes. This research supplies new knowledge, theories, and concepts for a host of diseases, including arthritis.

Diseases such as rheumatoid arthritis, lupus, and related disorders are characterized by widespread alterations, including inflammation, of connective tissue. Because collagen is the major protein of connective tissue, cartilage, and bone, studies aimed at understanding the properties of this protein will help scientists learn more about arthritis and related diseases.

Dr. Frederick Silver, an NIGMS grantee at Rutgers Medical School, is studying the mechanisms of collagen fibril formation in test-tube systems and in animal tissues. Collagen fibrils, long cable-like structures that are often grouped in larger bundles, are the most common type of connective tissue fibers. They compose the main mass of such structures as tendons, ligaments, and the intercellular substance of bone and cartilage.

Dr. Silver is using light-scattering techniques to help determine the structure of the collagen molecules, and electron microscopy of various tissues to visualize the relationship between these molecules (while they are in the process of assembling into fibrils) and cell surfaces. He has found evidence of a difference in the mechanisms by which different tissues form collagen fibers. If this proves to be true, it may be helpful in sorting out how the various collagen diseases develop.

Another NIGMS grantee, Dr. Joan Steitz, and her coworkers at Yale University in New Haven, Connecticut, are using sera from patients with autoimmune disorders, particularly lupus, to characterize and determine the structure and function of molecules called small ribonucleic acid protein particles (RNP's). Several types of antibodies react with RNP's in test tube systems.

Dr. Steitz is using these antibodies to help determine the structure of the RNP's. Antibodies that bind with one RNP have been found to inhibit splicing of mRNA (messenger RNA--the molecule that transmits genetic information from the cell nucleus to the cytoplasm, where it directs protein synthesis) in cells. Splicing of the mRNA molecule is an essential step in the process by which the genetic message is transcribed--in turn a step toward translation of the message into protein. This finding is the first direct evidence of the role of RNP's in splicing reactions.

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Although Dr. Steitz is using antibodies in the sera of lupus patients to learn more about how basic cellular processes are carried out, knowledge gained from these studies will eventually contribute to our understanding of many diseases, especially autoimmune disorders.

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National Institute of Child Health and Human Development

NICHD supports and conducts research on collagen and bone disorders as well as disorders of the immune system.

Studies by intramural scientists Drs. Michael Zasloff and Joan Marini focus on fibrodysplasia ossificans progressiva (FOP). FOP is a rare congenital disease that causes muscle pain and swelling as muscle tissue is gradually replaced by bone. The researchers have found that Tc99 bone scans and CT (computed tomography) scans can delineate the progress of ossification. In addition, CT scans have actually shown new bone developing within the fascia (membrane that separates and envelops muscle) indicating that FOP develops there rather than within muscle itself.

Looking for chemical changes associated with the disease, Dr. Zasloff and colleagues verified earlier reports that certain prostaglandins (a family of hormone-like substances that, among other actions, modulate inflammation and immune responses) are associated with FOP. This past year plasma levels of the prostandin PGE_2 were measured in 25 patients, all of whom had markedly high levels of this compound. These patients were also found to have the highest levels ever measured in humans of bone morphogenic protein. It can induce bone formation in man and other vertebrates. These findings have broad implications for our understanding of FOP and of normal bone formation in man.

The researchers are continuing a study to determine the most effective treatment for FOP. A synthetic retinoid, or vitamin A derivative, has been found to reduce the appearance of new ossification centers.

Dr. Zasloff and colleagues have also begun new studies of collagen molecular biology and its relation to human bone disease. The focus of research is osteogenesis imperfecta (OI), an inherited condition. Tissue and blood samples of OI patients are being collected and analyzed to obtain information on the hereditary material DNA and RNA. The researchers are working to pinpoint the molecular basis of this disease as well as the normal mechanisms involved in bone development and growth. Earlier research by this group pointed to the polypeptides (precursors of protein) within collagen itself as the source of the defect. Their latest results indicate that a chemical difference in polypeptides does in fact occur in OI victims. Their findings may contribute to the development of a treatment for OI as well as for other human diseases affecting connective tissue.

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The development of arthritis is an early symptom of lupus. Dr. Sara Walker at the University of Missouri at Columbia, under contract to NICHD, is investigating the effects of various estrogens and progestins on a mouse model (mice) for lupus. She is analyzing death and morbidity rates for treated and untreated mice to ascertain whether various kinds of treatment give survival advantages. This study will offer insight into the best choice of steroids for women suffering from lupus.

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National Institute of Environmental Health Sciences

Lead poisoning can produce diverse symptoms including renal toxicity and gouty arthritis (saturnine gout). At the University of Tennessee at Knoxville, Dr. Walter R. Frakas, a National Institute of Environmental Health Sciences (NIEHS) grantee, is examining how lead affects enzymes responsible for purine metabolism. Because purine changes are found in patients suffering from gouty arthritis, this work may help clarify how this disease originates. Recently Dr. Frakas has shown that the activity of guanase, a purine metabolism enzyme, is inhibited by low lead ion levels. The role of guanase is to convert guanine to xanthine. Since guanine is very insoluble, lead poisoning may cause an accumulation of guanine precipitates. Using a pig model, lead poisoning was found to induce a fivefold increase in guanine in the extracellular fluid, and crystalline concretions identified as guanine were observed in the region of the femoral head. This study has been extended to primates since purine metabolism in primates and humans is somewhat different than in lower mammals. The investigator found that marmosets that exhibited lead poisoning also had elevated guanine levels in the urine. Thus, these data also implicate altered purine metabolism in the etiology and saturnine gout.

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National Institute on Aging

The National Institute on Aging (NIA) supports research on biomedical, social, and behavioral conditions that affect the aging process. Certain types of arthritis are prevalent in older persons. Osteoarthritis (OA)--a degenerative joint disease--occurs in relatively few individuals under age 20 but about half of the population over 60 experiences symptoms.

The cause of OA is not known, although research conducted over the years has produced basic knowledge that clarifies a number of mechanisms underlying the disease. For example, cartilage in persons with severe symptoms of OA has been recognized as being different from cartilage in persons without symptoms.

Dr. William Horton, an NIA grantee at the University of Texas in Houston, is studying the repair process of OA by examining cartilage from patients with various chondrodystrophies. These are a group of rare, inherited cartilage disorders characterized by dwarfism and the tendency to develop OA. Dr. Horton has found that many of the chondrodystrophy cells responsible for repairing osteoarthritic cartilage closely resemble normal cartilage cells. Thus, these osteoarthritic cells produce, at one stage of development, altered cartilage that may be unusually susceptible to degeneration. Dr. Horton's studies should provide insight into abnormal changes in cartilage cells and, possibly, new approaches to therapy. Dr. Horton is currently trying to identify factors that affect the development of OA cartilage cells and to identify how the altered tissue differs from that found in normal joint cartilage.

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Division of Research Resources

When administered regularly, low doses of the anticancer drug methotrexate appear to relieve many of the painful and crippling symptoms of rheumatoid arthritis.

A study on methotrexate was conducted by Dr. Marshall M. Kaplan and colleagues at the New England Medical Center General Clinical Research Center (GCRC) in Boston, Massachusetts. The New England Medical Center GCRC is one of 78 such facilities supported by the NIH Division of Research Resources, 48 of which are conducting research on arthritis. Results of the study indicate that, in the absence of alcohol consumption, low doses of methotrexate taken on a weekly basis rarely cause clinically significant liver damage, although high doses of the drug are associated with liver damage when administered to cancer patients.

Liver biopsies were performed on 30 patients with a range of noncancerous diseases before they were given the methotrexate. When pretreatment liver biopsies were compared to those performed on the same patients after 1, 2, and sometimes 3 or 4 years of continued methotrexate treatment, 26 patients showed no liver damage.

The results suggest that methotrexate is only minimally toxic to the liver. Its effectiveness in the treatment of patients with certain forms of arthritis and psoriasis may thus outweigh the risks associated with its use. Because routine blood tests are not adequate to detect liver damage, the GCRC researchers recommend that patients taking methotrexate on a regular basis undergo liver biopsies at 1- or 2-year intervals. Consumption of alcohol, which may increase the risk of liver damage associated with methotrexate use, should be discouraged in patients taking the drug.

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Outlook

Building on resources and knowledge that exist today, researchers are increasingly confident that they can discover the causes of arthritis and related musculoskeletal diseases. NIH and private voluntary organizations have developed a strong and enduring partnership committed to arthritis and musculoskeletal diseases research. This concerted national effort will ensure continued progress toward more effective methods of treating and, ultimately, preventing these diseases and will significantly improve the health of the American public.

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